SCREENING OF CARBAMAZEPINE-IBUPROFEN (CBZ-IBU) CO-CRYSTAL FORMATION USING STOICHIOMETRIC METHOD

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ABSTRACT

A research was conducted on the screening of carbamazepine-ibuprofen co-crystal formation using stoichiometric method via co-grinding and solvent evaporation. Pharmaceutical co-crystals formation have been proven useful in enhancing the solubility, dissolution rate, stability, and bioavailability of APIs and recognized as the promising alternative to improve APIs properties. Thus, the purpose of this research is to determine the co-crystal formation of carbamazepine-ibuprofen (CBZ-IBU) using stoichiometric methods. In this method, two techniques are used which are solvent evaporation and co-grinding by using ethanol, acetonitrile, ethyl acetate, propanol and formic acid as a solvent. Then, the produced crystal was characterized using differential scanning calorimetry (DSC) and optical microscopy. From this research, it is shown the morphology of the crystals obtained shows prismatic blade like (isometric) morphology indicated that these crystals refer to IBU confirmed by DSC results. The findings concluded that co-crystal was not being able to be formed via these methods of screening.

ABSTRAK

Satu penyelidikan telah dijalankan untuk mengkaji saringan terhadap pembentukan ko-kristal carbamazepine - ibuprofen (CBZ-IBU) menggunakan kaedah stoikiometri melalui dua teknik iaitu pengisaran dan penyejatan pelarut. Ko-kristal farmasi telah terbukti berkesan untuk meningkatkan keterlarutan, kestabilan, dan bioavailabiliti API dan diiktiraf sebagai alternatif yang boleh meningkatkan kualiti API. Oleh itu , tujuan kajian ini adalah untuk menentukan pembentukan ko-kristal CBZ – IBU menggunakan kaedah stoikiometri. Dua teknik telah digunakan iaitu penyejatan pelarut dan pengisaran dengan menggunakan ethanol, acetonitrile, ethyl acetate, propanol and asid formik sebagai pelarut. Kemudian , kristal yang dihasilkan di analisa menggunakan differential scanning calorimetry (DSC) dan mikroskop optik. Bentuk hablur kristal yang diperolehi daripada kajian ini menunjukkan bentuk seperti bilah prisma (isometrik). Bentuk hablur Kristal ini menunjukkan bahawa kristal ini merujuk kepada IBU dan telah disahkan oleh keputusan DSC. Kesimpulannya, kristal tidak dapat dibentuk melalui kaedah saringan ini .

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LIST OF ABBREVIATIONS

APIs	Active Pharmaceutical Ingredient
CBZ	Carbamazepine
IBU	Ibuprofen
DSC	Differential scanning calorimetry
TGA	Thermogravimetry Analysis
PXRD	Powder X-ray Diffraction
FTIR	Fourier Transform Infrared
SEM	Scanning Electron Microscopy
EX	*Exemestane*
MA	Megestrolacetate
NCT	*Nicotinamide*

Greek

Δ_{fus}h (J/g)	Entahalpy fusion
T_m (ºC)	Melting point
(ºC)	celcius
ml	milimeter
µm	micrometre
cm	centimetre

1 INTRODUCTION

1.1 Motivation and statement of problem

Physiochemical properties of co-crystals are of great attention for the development of APIs. Pharmaceutical co-crystals become the motivation for drug development in the adjustment of the physiochemical properties to improve efficacy of a dosage form and the overall stability (Blagden et al., 2008). For most of the properties of co-crystals, when measured, has a value that lies between co-former and pure drug. The prior statement is supported by the data of melting point analysis of co-crystals, which often is found to be in between pure drug and co-former. From stability point of view, co-crystals are balance with regard to storage conditions and moisture under normal processing (Blagden et al., 2008).

Besides, pharmaceutical co-crystallization also can enhance the solubility of poorly water soluble drugs. Pharmacology activity of the API does not affect when co-crystallized with pharmaceutically acceptable (GRAS) compounds but it can boost their physical properties like bioavailability and solubility (Zaworotko, 2008). Solubility of co-crystal product is often more than that of pure drug but less than that of co-crystal former. However, this is not usually the case since there has been evidence of reduced solubility of the co - crystal product in corresponding to the API. If solubility of the co - crystal product is increased in corresponding to the API, intrinsic dissolution is also improved for co-crystals in corresponding to pure drug and vice versa.

Over for the three decades, Carbamazepine (CBZ) has been an important antiepileptic drug. CBZ faces multiple challenges of oral administration for lower solubility of water with high quantity required for curative effect, auto induction for metabolism and limited bioavailability. Meanwhile, Ibuprofen (IBU) or propanoic acid is known as anti-inflammatory drug. It is usually used as an analgesic or for the relief of fever and arthritis. IBU has less soluble in water. It is shown that CBZ and IBU solid compound faces the same problem such as having low solubility. Both of the compounds have low solubility in water but IBU is less soluble in comparison to the CBZ. In contrast, CBZ is less soluble in solvent in comparison to the IBU.

Therefore, IBU acts as co-former where the CBZ act as API because IBU more soluble in comparison to CBZ in solvent. Solubility is important to deliver drugs to patient in safe and an efficient and cost effective manner. If the drug has low solubility, it will difficult to be absorbed from the gastrointestinal tract into the blood stream and influence the site of action (Junghanns & Muller, 2008). Therefore, improve solubility also can optimize the bioavailability.

1.2 Objectives

The following are the objectives of this research:

- This work aims to screen the CBZ-IBU co-crystal formation using stoichiometric method via evaporation and co-grinding.

1.3 Scope of this research

The following are the scope of this research:

i) Screening co-crystal using stoichiometric methods with different solvents.

ii) Characterization crystal produced using DSC and optical microscopy.

1.4 Organisation of this thesis

The structure of the reminder of the thesis is outlined as follow:

Chapter 2 is about literature review on the type of co-crystal, pharmaceutical co-crystal, molecular interaction with the pharmaceutical co-crystal, the formation method and co-crystal characterization technique. In this section, all the relevant journals, technical paper and books taken from those researches will be studied and discussed.

Chapter 3 will be covered the part of experimental set up and will be explained in more details on methodology and operating procedures. The co-crystal formation method and characterization techniques used for this system are described in detail. In addition, in this chapter also explained the material used in this experiment.

Chapter 4 will be covered in the results and discussion of the research during the operation process. All the experimental result and data will be discussed in details which are included screening methods and characterization of crystal produced.

Chapter 5 will be discussed in the conclusion can be made for the study and some recommendations can be taken. Figure 1.1 shows the road map of the thesis.

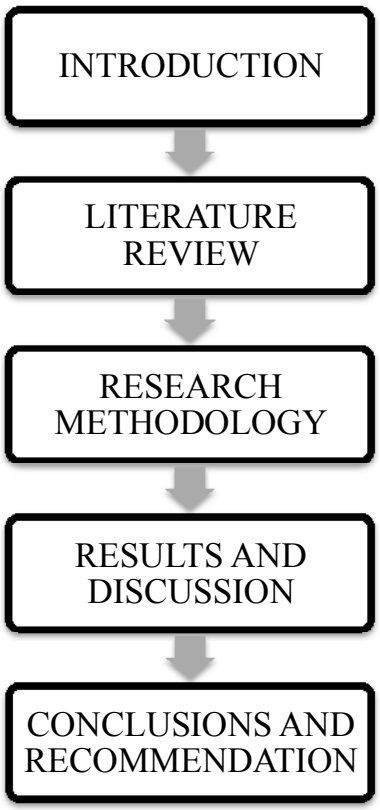

Figure 1-1: The road map of thesis

2 LITERATURE REVIEW

2.1 Overview

This chapter describes about the type of co-crystal, pharmaceutical co-crystal, molecular interaction with the pharmaceutical co-crystal, the formation method and co-crystal characterization technique.

2.2 Introduction

A co-crystal can be described as crystalline structure consists of two or more organic element, where the element may be atoms, ions or molecules which all elements are solid form at room temperature in a stoichiometric ratio. It is also involves interactions of non-covalent like ionic bonds, van-der Waals bonds or hydrogen bonds, in a crystal lattice (Shan and Zaworotko, 2008). According to Vishweshwar et al., in 2006 if one of the candidates is a pharmaceutically active ingredient, they are referred to as pharmaceutical co-crystals.

Active pharmaceutical ingredients (APIs) are usually delivered to the patient in the solid form as part of an acceptable quantity form (e.g., tablets, capsules, etc.). Solid form is the preferred state rather than amorphous because it is mainly most stable crystalline form of the compound (Morissette et al., 2004). There are several of different solid forms that APIs can exist, such as solvates, hydrates, amorphous solids, polymorphs, salts, and also co-crystals as shown in Figure 2.1. All of these forms show physical and chemical properties that can greatly impact the stability, bioavailability, solubility and other performance characteristics of the drug (Byrn et al., 1999).

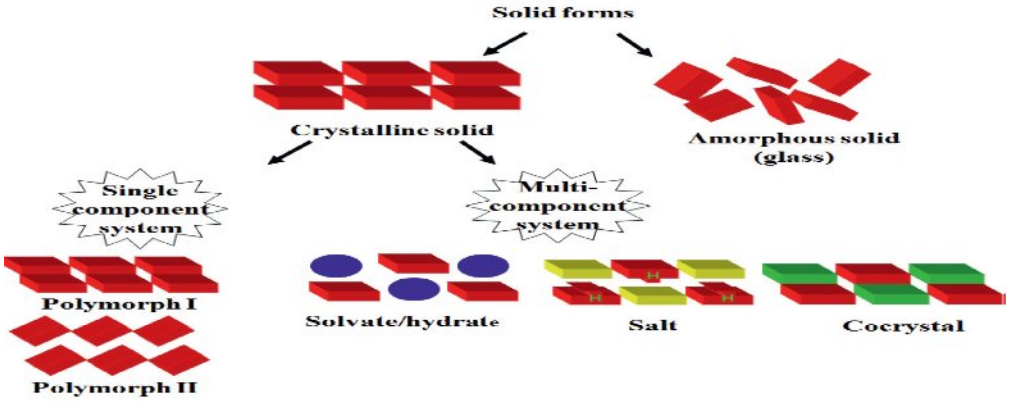

Figure 2-1: Possible solid form of a drug. Red, blue and green represent drug, water/solvent, counter ion, and co-former molecules respectively (Byrn et al., 1999)

Solvate is defined when one candidate is a liquid at room temperature but if both candidates are solids at room temperature; the crystals are defined as co-crystals (Morissette et al., 2004). Usually, solvate crystals are unstable which lead to less soluble forms impact from the loss of solvent that may ahead to the amorphous phase crystallizing and also from the desolvation during storage.

Salt formation is form from reaction between an acid-base of the APIs with an acidic. However, this approach has a limitation, which is the API must have a suitable (basic or acidic) ionizable site. In contrast, co-crystals offer a different access resulted by freely reversible with non-covalent interactions, where any API are not considered the acidic, basic or ionizable groups. Therefore, it could conceivably be co-crystallized. In addition, when salts are formed, the proton is fully transferred while, for co-crystals, there is no transfer or only an incomplete transfer (Aakeröy et al., 2007).

Meanwhile, polymorph is defined as a solid crystalline phase that would have the same compound with difference crystalline form (McCrone, 1965). Polymorphs may spontaneously convert to the stable form from a metastable form (unstable form) at a certain temperature. It also has different stabilities. In addition, they exhibit different solubility and melting points which impact the dissolution rate of drug. However, it is not usually straightforward to get a specific polymorph of a material (Bardwell et al., 2011). Moreover, highly polymorphic compounds also present variety challenges in development of drug.

Thus, co-crystallization is become first placed approaches to physical property optimization rather than polymorph, solvates, and salt selection. The co-crystallization offers a field for enhancing the biopharmaceutical and physicochemical properties of APIs throughout the development of the new class of crystalline solids, called pharmaceutical co-crystals (Shan and Zaworotko, 2008). Over the last decade, pharmaceutical co-crystals also has been growing interest in the design of drug, which arise as a potential method for improvement of stability, bioavailability and low water solubility of drugs (Qiao et al., 2011).

2.3 Previous work on Pharmaceutical co-crystal

Pharmaceutical co-crystal can be described as crystalline of multi-component which involve the active pharmaceutical ingredient (API) with other components are called co-former that are tied together in the crystal lattice through non-covalent interactions primarily hydrogen bond (Qiao et al., 2011). Some researchers have defined co-formers as stabilizers in co-crystallization process (Qiao et al., 2011). Liquids and solids may also serve the purpose of co-crystal former (Shan and Zaworotko, 2008). However, when co-crystal reactant components are solids under ambient conditions has useful benefits over liquid or gas co-formers. Co-crystals are constructing based on crystal engineering with following the principal of the supramolecular synthesis. Although, pharmaceutical co-crystal still not commercialized for use in the market but there are much work has been done for formation of the co-crystal such as carbamazepine, indomethacin and ibuprofen. Table 2.1 represents some example of pharmaceutical co-crystal.

Table 2-1: Example of pharmaceutical co-crystal

API	Co-formers	Methods	References
Carbamazepine	Saccharin	-Cooling crystallization	(Hickey et al., 2007)
Indomethacin	Saccharin	-Slow evaporation -Liquid-assisted co-grinding	(Basavoju et al., 2008)
Ibuprofen	Nicotinamide	-Slow evaporation -Slurry conversion	(Frederico et al., 2013)
Carbamazepine	Nicotinamide	-Slurry-based crystallization	(Gagnière et al., 2009)

2.4 Molecular interaction in co-crystal

Co-crystals are constructed based on supramolecular synthons. The term of supramolecular synthons is defined by Desiraju, in 1995 as a structural unit within supra molecules which can be connect by non-covalent interaction such as π-stacking, van der Waals force, hydrogen bonding, and halogen bonding. Meanwhile, Etter and Reutzel, in 1999 added in designing most of the pharmaceutical co-crystals the hydrogen bonds play a great role. In addition, Dale et al., 2004 also provided the guidelines to predict the formation of hydrogen bonds as follows: (i) in hydrogen bond formation, all good proton donors usually are used; (ii) intramolecular hydrogen bonds are preferred over intermolecular hydrogen bonds in a six membered ring; (iii) the best proton donors and proton acceptors remain after form intermolecular hydrogen bonds with each other from intramolecular hydrogen bonds. Carbohydrates, amides, carboxylic acids, amino acids and alcohols are the examples of pharmaceutically acceptable co-crystal formers that can be co-crystallize with target APIs as illustrated in Figure 2.2.

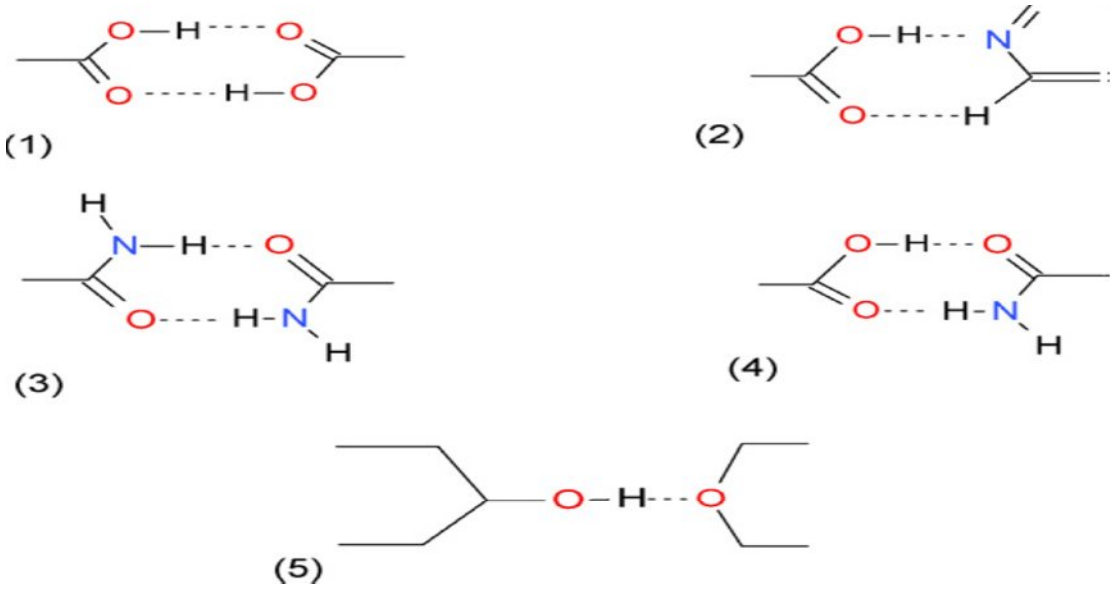

Figure 2-2: Typical hydrogen bonds utilized in crystal engineering (Qiao et al., 2011).

2.5 Physiochemical properties of co-crystal

Physicochemical properties of co-crystals are a combination of individual properties of both drug and co-crystal former. These properties of a co-crystal need to be investigated in order to determine the performance in the marketed dosage form (Bryn et al., 1999). In the beginning development of drug, these properties, such as bioavailability, stability, melting point, and also solubility greatly important when forms a new compound, such as a co-crystal.

2.5.1 Melting point

The melting point is indicated by the temperature at which the solid phase achieved equilibrium with the liquid phase. Schultheiss and Newman, in 2009 stated co-crystal have melting point in between the APIs and co-formers or lower than the APIs or co-formers. It is proving that, the APIs can be tuning through forming co-crystal. Meanwhile, Fleischman et al., in 2003 investigated the impact of crystal packing on the melting point of co-crystals. It is shows that although the four co-crystals had same heteromeric O–H•••N hydrogen bond, it had different overall packing arrangements and also different melting points.

2.5.2 Solubility

Solubility of co-crystal product is usually more than that of pure drug but less than that of co-former. However, the solubility of the co - crystal product can be reduced in comparison to the API. Intrinsic dissolution is also improved for co-crystals if the solubility of the co - crystal product is increased in comparison to the API, pure drug and vice versa. For example, Miroshnyk et al., in 2009 tried to improve the solubilities of two APIs, which is exemestane (EX) and megestrolacetate (MA). These samples are prepared from organic solutions with several particle sizes. It is shown that co-crystallization of the EX and MA enhanced the initial dissolution rates compared with the original crystals. In addition, the co-crystal of EX/MAL also showed a high dissolution rate even with large particles.

2.5.3 Bioavailability

Bioavailability is amount of extent of the active drug and the rate that attain the systemic circulation (Bermajo and Alvarez, 2008). The ultimate goal of the co - crystal

investigation is to enhance the bioavailability of an API. For example, animal bioavailability needs to analyse when preparing new forms of a compound because it is an important parameter but there are restricted numbers of animal bioavailability researches on co-crystals. A dog study based on Hickey et al., in 2007 was compared a 1:1 of mole ratio between CBZ and saccharin co-crystallized with the marketed tablets of carbamazepine. It is shows the pharmacokinetic parameters obtained to be similar to the present marketed product.

2.6 Analysis methods for co-crystallization

Co-crystals formation can be categorized into liquid and solid based methods. Solid-based method for co-crystal formation such as co-grinding usually refer on the stoichiometric ratio of the APIs and co-former, while the liquid-based methods may can be either non-stoichiometric ratio (reaction crystallization and slurry) (Alhaweh et al., 2010, Zhang et al., 2007) or stoichiometric ratio (solvent evaporation crystallization and spray drying) (Alhalaweh et al., 2010)

2.6.1 Solvent evaporation

In this method, the APIs and co-former are taken in an appropriate equal amount and dissolved in a solvent and the solution was allowed to evaporate at the room temperature. This solvent evaporation technique works only when different molecules of complimentary functional group afford hydrogen bond that are more favorable than each of the individual components and its tend to be thermodynamically favored (Jayasankar et al., 2006). There are many successful co-crystal examples were obtained by this method such as Indomethacin–saccharin co-crystal (Basavoju et al., 2008).

2.6.2 Cooling crystallization

Cooling crystallization method used different of temperature to achieve the crystallization system, which has much potential of a large scale for the co-crystals production. Crystals produced will precipitate when the solution becomes supersaturated with respect to co-crystal as the temperature drops down (McNamara et al., 2006). For example, co-crystallization of carbamazepine and nicotinamide (CBZ/NCT) was studied by Gagniere et al., in 2009, which the solid phase evolution during the cooling co-crystallization process was monitored by an in situ video probe.

2.6.3 Co-grinding

Co-grinding can be divided into two different techniques that is dry and liquid-assisted grinding. Neat grinding or dry grinding involve with mixing the APIs and co-former in the stoichiometric ratio and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill. This method needs one or both APIs and co-former exhibiting significant vapour pressures in the solid state (Friscic and Jones, 2009). Meanwhile, small amount of suitable solvent are added in the mixture while grinding for the liquid-assisted grinding methods. There are many kinds of pharmaceutical co-crystals that have been successfully synthesized by using neat grinding method such as Indomethacin- saccharin co-crystal (Basavoju et al., 2008).

2.7 Analysis characterization for co-crystal

Co-crystal characterization is also an important part in co-crystal development. There are many type of instrument that can be used to characterized the crystal produced such as optical microscopy, differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscopy (SEM) and raman spectroscopy.

2.7.1 Optical microscopy

The basic physicochemical crystal size at preliminary level may be evaluated by optical microscope using stage micrometer and eyepiece micro meter (Abramowitz et al., 2002). It is used the fundamental system of lenses and visible light to magnify images of small samples or particles. The basic optical microscopes are very simple, compared to the modern designs which are only aim to improve resolution and sample contrast. A micrograph was generated when the image taken from an optical microscope that captured by normal light-sensitive cameras (Abramowitz et al., 2002).

2.7.2 Differential scanning calorimetry (DSC)

DSC is the most widely used technique for the thermal property testing of co-crystals. The differential scanning calorimetry is a characterization method based on the heat of reaction involved in different thermal events. In the pharmaceutical industry, the DSC is mostly used to obtain melting points of the API and thus, determine its purity (Oberoi et al., 2005). It shows there is a clear difference between the melting point of the co-formers and the co-crystal itself when the co-crystal was analyzed. It is a technique that

can be used for qualitative and quantitative analysis, because the heat of the reaction is directly proportional to the mass quantity of the compound analyzed (Yamashita et al., 2013). However, by being a destructive technique, the thermal events that occur with the material can interfere with quantitative measurements, essentially on polymorphs and co-crystals.

2.7.3 Powder X-ray diffraction (PXRD)

The Powder X-ray diffraction is used to determine the differences between the crystalline structures (Buanz et al., 2011). The presence of a new crystallographic motif can be distinguished using this technique, which can be a polymorph or a co-crystal (Croker et al., 2012). It is a non-destructive method and presents diffraction patterns unique for each structure. However, it is a challenging method to implement in PAT systems. Besides, the quantitative analysis can only be made with the internal standard addition method or by mixture analysis, and its data can present problems due to preferential orientation and different crystal granulometry, which make the quantitative analysis difficult to perform (Chieng et al., 2011).

2.7.4 Scanning electron scanning (SEM)

Scanning electron microscope used a high-energy beam of electrons in a raster scan pattern to take the images of sample. It is usually used to determine micrograph of the co-crystal particle size (Basavoju et al., 2008). This technique very useful especially to distinctive the differences in their crystal habits because it allows characterization of surface morphology of materials. It also offers some advantage for the characterization of incompatibilities of materials when SEM studies were combined with other thermal and spectroscopic techniques, such as FT-IR, DSC and HSM (Bikiaris et al., 2005).

2.7.5 Raman spectroscopy

Raman spectroscopy has been demonstrated to be a powerful tool for distinguishing isostructural phase. It is used to observe the rotational, vibrational and other low frequency modes in a system. Moreover, it is also an alternative method to identify crystalline arrays of several pharmaceutical drugs (Burley et al., 2012). In addition, it is a quick technique, non-destructive, presents much chemical information and lower detection limits when compared to XRPD and DSC (De Beer et al., 2011). However,

the fluorescence phenomena can make the analysis of some samples difficult, and micro-Raman usually presents a small laser spot, leading to sampling problems (Shin and Chung, 2013).

2.8 Summary

In conclusion, from the previous study, it is shown that co-crystal formation can be form from stoichiometric or non-stoichiometric methods. The co-crystal produced also can be analysed using thermal or spectroscopic techniques. It is shows that the co-crystallization technology can enhancing the pharmaceutical properties such as habit, bulk density, compressibility, solubility, melting point, variability, hygroscopy, and dissolution rate rather than the traditional approaches such as solid dispersion or salt formation.

3 MATERIALS AND METHODS

3.1 Overview

This chapter describes the materials use and the methodology applies during this research. This research intends to achieve two main goals which are preparation procedure of CBZ-IBU co-crystal and to identify physical characteristics of CBZ-IBU co-crystal.

3.2 Chemicals

A chemical used for the screening were obtained from various sources namely ECA International Corporation (Carbamazepine 99%) and Shasun Pharmaceuticals (ibuprofen SN grade).

3.3 Solvents

A solvent used for the screening were obtained from various sources namely Fisher chemical (Acetonitrile HPLC grade, Acetone analytical reagent grade), Sigma-Aldrich (Propanol, Ethyl acetate, Formic acid, 99.5%) and Merck Malaysia (ethanol gradient grade).

3.4 Preparation of the co-crystal

3.4.1 Solvent evaporation

CBZ-IBU co-crystal was crystallized using the solvent evaporation method. A mixture of CBZ and IBU (1:1 mole ratio) was dissolved in a 25 ml of ethanol in 50 ml of conical flask and heated to 30℃ in incubator shaker for 1hr. If some of the solute of CBZ and IBU would not dissolve after one hour, 2 ml of ethanol was added until it did so. Once the solute of CBZ and IBU had dissolved, another 10 ml of ethanol was added again in the solution. The solution was left in the incubator shaker to equilibrate for 24 hour. After 24 hour, solution of CBZ and IBU was withdrawn from the conical flask using a syringe filter to remove any impurities. The solution was filled in the 20 ml vial and covered with parafilm, with a few small holes was poked in it. The solution was left to evaporate at room temperature until the crystal appears. After the crystal appears, the produced crystal was filtered using the vacuum pump. The produced crystal are dried at

room temperature for 24 hour and kept in a vial prior to characterization using differential scanning calorimetry (DSC) and optical microscopy (Abd Rahim et al., 2013). The experiment was repeated using different solvent such as propanol, ethyl acetate, formic acid and acetonitrile and was repeated three times for each of solvent. The produced crystal was characterized using differential scanning calorimetry (DSC) and optical microscopy.

3.4.2 Co-grinding

The co-grinding method was conducted in a dust extraction hood and manually ground using a mortar and pestle for 10 minutes. In dry co-grinding, 50 mg of CBZ and 40 mg of IBU was prepared in combination of 1:1 ratios. The CBZ and IBU was ground using a mortar and pestle for 10 minutes while in wet co-grinding, 2 drops of ethanol was added while the sample was ground (Abd Rahim et al., 2013). The wet grinding experiment was repeated using different solvent such as acetonitrile, formic acid, ethyl acetate and propanol. Each of the experiment was repeated for three times. The produced crystal was characterized using differential scanning calorimetry (DSC) and optical microscopy.

3.5 Preparation of characterization of crystal produced

3.5.1 Differential scanning calorimetry (DSC)

The formation of co-crystal via solvent evaporation, co-grinding were characterized by a Thermal Advantage DSC Q1000 (TA Instrument). A sample of the crystals produced (about 2.5 mg) was studied under a nitrogen purge (50 ml/min) and was heated (40-200ºC) at a scanning rate of 10 ºC/min. The sample was placed in aluminium pans and the lids were crimped. The melting point, heat of fusion and the onset temperature were obtained.

3.5.2 Optical microscopy

A Dino-eye microscope eyepiece and Carl Zeiss model microscope with series number of 3108016587 was used to observe the morphology of the crystal obtained from co-crystal screening. The images were taken with 771.7x magnification and at scale 1cm represent 25µm. The sample of co-crystal was placed at the slide using spatula. After that, the slide was placed at the microscope and the sample was observed using eye-

piece. The samples used for this measurement were taken after the samples were filtered.

4 RESULTS AND DISCUSSION

4.1 Overview

In this chapter, the findings obtained from screening study will be discussed which comprised of DSC and microscopy analysis.

4.2 Differential scanning calorimetry (DSC)

4.2.1 Pure component

Figure 4.1 shows a large endothermic peak (curve) at 190.75^{o} C and a small endothermic peak (curve) at a range between 155-165^{o}C. Whereas Figure 4.2 shows only one endothermic peak at 76.33^{o} C. These peaks were attributed to melting points of pure CBZ and IBU respectively. A small endothermic peak (curve) represents the melting point of CBZ form III. While, the large endothermic peak represents the melting point of CBZ form I. These two endothermic peaks (curve) represent the characteristics of CBZ form III (Grzesiak et al., 2003). CBZ form III is the form that commercially available because it is thermodynamically stable at room temperature. The melting points obtained from the DSC curves are similar to the values mentioned in the literature that is 75–78ºC (Rasenack and Muller, 2002) for the IBU while for CBZ in between 190-191 ºC (Wu et al., 2011). These values together with the accuracy of the melting peaks indicate a high purity of ibuprofen and CBZ. The melting point for pure CBZ and pure IBU are listed in Table 4.1.